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TITLE: The Comparative Efficacy of the Masquelet versus Titanium Mesh Cage
Reconstruction Techniques for the Treatment of Large Long Bone Deficiencies

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14. ABSTRACT The study comprises a single center, randomized, two-arm clinical trial conducted at the Department of Orthopaedic Surgery & Rehabilitation, University of Texas Medical Branch, Galveston, TX, with a primary objective to assess and compare the functional outcome of patients with large segmental bone defects reconstructed with the Masquelet technique (MT) versus the titanium mesh cage technique (TMCT). The secondary objectives include the radiographic determination of defect healing, and comparative assessment of cost and resource expenditures between the two techniques. From 24 patients with segmental defects presented to our institution throughout the trial period, 16 met the study eligibility criteria and were successfully enrolled, and they include 9 MT, 7 TMCT. Within the last 12-month study period, 8 patients were enrolled, 2 completed the study, 1 was withdrawn, and 11 are actively participating. Two patients (study subject #4 and subject #14) experienced adverse events AEs, of which one was related with the study and the subject was excluded from continuation in the trial as per study protocol. Both AEs have been reported to PI's IRB and DoD. So far, 11 study subjects (6 MT, 5 TMCT) are being actively followed, and their study courses are uneventful. There are 3 additional potentially eligible study patients identified. The trial is ongoing and patients' enrollment is in progress.					
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1. Introduction

The United States Department of Defense funds a clinical trial that can be a major improvement in the treatment of extremity trauma associated with segmental bone defects. These devastating injuries occur in both civilians and the military population. They typically result from motor vehicle accidents, high-energy fractures, gunshot injuries, and blast injuries, but also can be an outcome of iatrogenic segmental bone resections due to infection or tumor. Despite many recent advances in this area, achieving healing bone defect and restoring injured limb function has been extremely challenging. Standard treatment options are exceedingly complex, require highly specialized equipment and/or skills, and typically necessitate multiple surgical procedures over a protracted period of time. Furthermore, major complications frequently occur with all the standard options and return to acceptable limb function is typically rare, and, in many instances amputation is required.

The present clinical study addresses this issue by assessing and comparing two innovative surgical bone defect treatment techniques that can be significantly more effective than the standard treatment options for civilian and military patients with these conditions. One treatment method—the Masquelet technique—involves two-stage surgery. In the first stage, a biomembrane around the defect is induced by the application of a cement spacer. The second-stage surgery is performed 6-8 weeks later and consists of cement spacer removal and bone graft placement while preserving the biomembrane. The other method—the cage technique—has been developed by the study principal investigators (PIs), and comprises one-stage surgical procedure in which a cylindrical, fenestrated titanium cage is packed with bone graft and implanted in the defect. Initial clinical experience with both of these techniques has been very promising, and there have been no prospective clinical studies comparing these two novel defect treatment methods. The present study aims to address that void.

The study is a randomized two-arm, single-center clinical trial conducted at the Department of Orthopaedic Surgery and Rehabilitation, The University of Texas Medical Branch (UTMB) in Galveston, Texas. The trial's primary objective is to assess and compare the functional outcomes of patients with large segmental bone defects reconstructed with the Masquelet technique versus the cage technique. The trial's secondary objectives include the radiographic determination of defect healing and the comparative assessment of cost and resource expenditures between the two techniques.

2. Keywords

Critical-size bone defects;
Segmental bone defect reconstruction;
Masquelet technique;
Titanium mesh cage technique

3. Overall Project Summary

Study Continuation and Approvals/Amendments: The annual approval for continuation of clinical trial has been obtained from the UTMB Institutional Review Board (IRB on Mar 11, 2016. No time lapses occurred between the renewed IRB approvals.

There were a few amendments filed and approved by the UTMB IRB, and they include:

- 1) Changing study reimbursement language to reflect the use of the reloadable VISA ClinCard system which replaced previously used Gift Cards (submitted to IRB on Jan 26, 2016; approved by IRB on Jan 29, 2016);
- 2) Removing Rickeedah Gitry from the study personnel (submitted to IRB on Jan 26, 2016; approved by IRB on Jan 29, 2016);
- 3) Request for annual renewal of the study by the UTMB IRB (filed to IRB Mar 4, 2016; approved by IRB on Mar 11, 2016);
- 4) Request to add Safee F. Ahmed as a primary study coordinator and change the role of Kirti Singh as a backup coordinator in the study personnel (filed to IRB on April 19; approved by IRB on April 24, 2016).

Overall, the study has been progressing without issues throughout all of its stages: identifying, recruiting, consenting, and enrolling the study eligible patients as well as the study surgical interventions, and the followup visits. No deviations from the protocol have been noted.

Adverse Events:

Two adverse events (AEs) have occurred in two study patients since the last annual report.

- 1) The first AE occurred on Feb 14, 2016 and it has been reported to the UTMB IRB and DoD on Feb 22, 2016. This AE involved the study subject TRIAL: 04-02/14 who received both stages of the Cage defect reconstruction and presented with the AE just 3 days before completing the 18-month final trial follow-up. The patient was a 47-year-old female, who on Feb 14, 2016 presented to ER with pain and swelling of her right upper arm, in the biceps area, and mild fever. The history and clinical exam were indicative for infection. Right upper arm was swollen, hard on palpation, pink in color, and warm to touch. Patient reported intermittent fevers over past 3 weeks reporting temperatures ranging from 101-103F. Patient was admitted to hospital, and scheduled for surgery next day. The surgery was performed under general anesthesia. The patient was positioned supine and the right arm area prepped and draped in standard sterile fashion. Antibiotics were held. Posterior triceps splitting through previous incision was made. A large collection of purulent material was encountered at the distal aspect of the incision that tracked deep to the hardware and bone. Cultures of aerobe, anaerobe, AFB, fungus were taken and sent to the lab. Superficial fat and muscle were dissected, and deep fascia was split. Scar tissue was carefully dissected deep, and radial neurovascular bundle was identified and protected throughout the case. The posterior plate was identified and removed, and then the medial plate also removed. Fluoroscopy confirmed removal of hardware. The distal one-third of the cage had fully incorporated, the proximal one-quarter of the cage also fully incorporated with the adjacent bone. The cage could only be removed by using oscillating saw to cut through bone at the proximal and distal ends of the cage. The cut-out cage with the bone was removed. Subsequently, the wound was irrigated with 9 liters of saline. Vancomycin-impregnated beads were then made and 4 beads were implanted into the humerus. Then, the fascia was closed with 0 PDS, subcutaneous was closed with 2-0 PDS, and the skin was closed with staples. The wound was dressed with Xeroform, 4x4, soft roll, and a posterior splint. Hemostasis was maintained throughout the case. The patient was extubated without problem. The patient was taken to the PACU in a stable condition. At the admission patients was positively tested for presence of illegal street drugs (amphetamine). Due to the nature of the AE patients has been removed from the continued participation in the study.

2) The second AE occurred on Aug 3, 2016 and it has been reported to both UTMB IRB and DoD on Aug 9, 2016. It involved the study subject TRIAL: 14-06/16) who had completed both stages of the Masquelet defect reconstruction (study Arm I). The patient was a 57-year-old male who on Aug 03, 2016, presented to the ER with fever with maximum reported temperature of 104. The patient reported having low-grade fevers at home and also mentioned that he accidentally removed the IV line and re-introduced it back to the vein by himself. Patient also reported removing his splint at home. Denied numbness/tingling distally in this left arm. The study physician saw and examine the patient that day in the clinic where further diagnostic tests were ordered. At evaluation of the CXR/CT chest multiple scattered lesions in lungs were seen which were interpreted as possibly being septic emboli. PICC line was removed and blood cultures obtained. There were no signs of surgical site infection as initially seen. Patient was informed that he will be called with the results and he was discharged from the ER. Culture results came in and confirmed gram negative bacteremia with Enterobacter. Patient was called immediately and recommended hospitalization. Patient was admitted, where he was treated with IV antibiotics and stabilized. On Aug 09, 2016, the patient has being discharged with oral antibiotics and good prognosis. This event has been recorder in the study files and it did not affect the patient's participation in the study.

The current status of the study:

A total of 16 patients have been enrolled in the study, of which 2 were withdrawn (subjects #2 and #3) as reported in the previous annual report, and 1 subject #4 due to AE. So far 2 study subjects uneventfully reached the 18-month study foldup, and thereby met the terms for study completion. The table below depicts current patient participation in the trial to date:

Trial Arm	Total Trial Subjects Enrolled	Subjects Completed Trial Uneventfully	Subjects Actively Participating	Subjects Removed from Trial Continuation
Masquelet	9	2	6	1
Cage	7	0	5	2
Total:	16	2	11	3

Within the last 12-month period encompassing the present annual report, 2 patients completed the study, 4 patients continue follow-up, and additional 8 were successfully enrolled. As previously stated, there were 2 AEs, and one of them resulted in study discontinuation. All other study subjects are being followed uneventfully as per the study protocol. There are 2 patients who await their index surgical defect reconstruction procedures. A total of 8 patients have received their respective surgical treatments for segmental bone defects in combination with a specific bone grafting option as per study randomization; they are all actively being followed for the designated study time points, ie 2 weeks, 6 weeks, 3 months, 6 months, 12 months, and 18 months.

Patient Enrollment and Follow-up:

Overall, patient enrollment in the trial has increased, but progresses at a rate slower than anticipated. Over the last 12-month period, a total of 11 patients with segmental defects presented to our institution. Among these patients were 3 civilian prisoners who met the study clinical eligibility criteria but could not be enrolled because PI's institutional IRB disapproved

participation of this vulnerable population; the other 2 patients were free-world patients with segmental defects; they will be approached for study participation once they meet/agree to the institutional criteria/policy for the treatment. The remaining 6 patients met all the study eligibility criteria, and they were all successfully enrolled, and subsequently randomized to the respective study treatment arms. Four of them received the respective surgical treatments, and are currently being followed up as per the study protocol; two await the scheduled respective surgical defect reconstructions as per study protocol. The two patients who successfully completed the trial are:

- (1) **Trial Patient #1:** A 67-year-old male with segmental bone loss in the distal femur as a result of an accidentally, self-inflicted, close-range, high-caliber civilian gunshot injury. The patient was randomized to study Arm I and received the two-stage Masquelet defect reconstruction procedure in combination with a Reamer-Irrigator-Aspirator (RIA) bone graft (Option A) according to the study protocol. The patient has completed all 6 required study followup visits (ie 2w, 6w, 3m, 6m, 12m, and 18m), and thereby reached the study endpoint. The patient's followup has been uneventful throughout the course of the treatment, and the patient has demonstrated very successful functional and radiographic defect treatment outcomes.



Fig 1. A short-range, high-caliber gun shot injury to the supracondylar portion of the femur (A) was initially treated with a fixed-angle condylar screw-plate construct. An infected nonunion developed, and infected bone was excised and the resultant segmental defect was treated using 2-stage Masquelet technique with RIA bone grafting and double-plate stabilization. The defect healing progressed uneventfully and graft consolidation was evident at 16 months post-surgical radiography (B,C) and computed tomography (D,E,F).

(2) Trial Patient #5: A 58-year-old female presented with a humerus segmental defect temporarily stabilized with an external fixator. This patient was enrolled and randomized to study Arm I, and received the two-stage Masquelet technique in combination with an RIA-harvested bone graft (Option A) according to the study protocol. The patient completed all required study followup visits (2w, 6w, 3m, 6m, 12m, and 18 m), and reached the study endpoint. The patient's followup was uneventful throughout the study. The patient's treatment demonstrates very successful functional and radiographic defect treatment outcome.

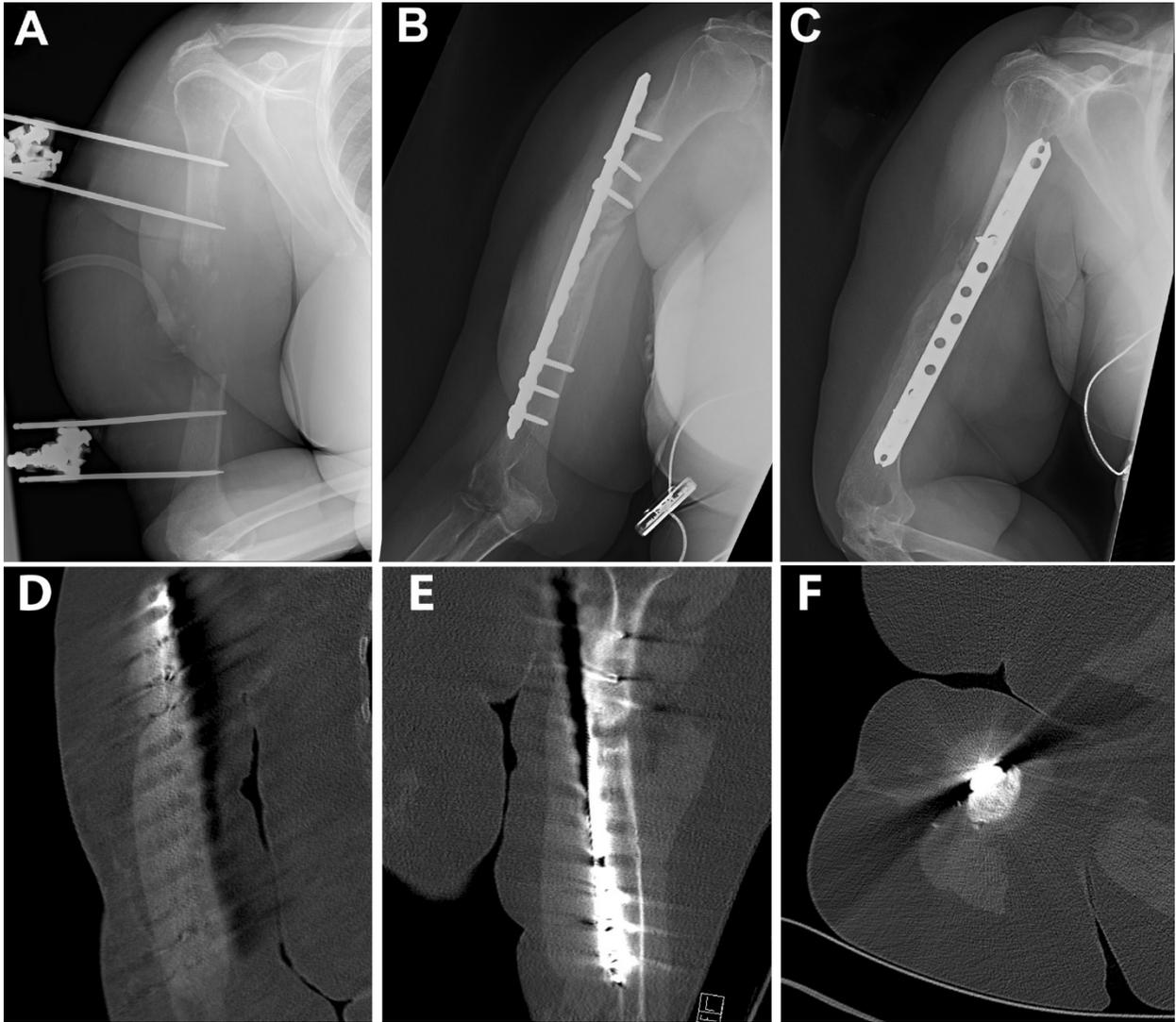


Fig 2. An infected nonunion of the humerus midshaft was treated with intravenous antibiotics and infected bone excision. The resultant large iatrogenic defect (A) was with two-stage Masquelet technique in combination with RIA-bone grafting and a locking plate-screw stabilization. Graft consolidation and defect healing are evident at 16 months post-surgical reconstruction on plain radiography (B,C) and computed tomography (D,E,F) .

A representative patients from the cage group (trial Arm II) who is near study completion:

Trial Patient #6: A 59-year-old male presented with infected nonunion in the tibia as a result of open fracture in an example of the cage reconstruction procedure. The patient was recruited into the study, and randomized to receive the cage technique for defect

reconstruction in combination with allograft cancellous croutons-DBM composite (Option B). He has completed three study followup visits (2w, 6w, 3m, 6, and 12m), and is currently at 3 weeks away from reaching his trial endpoint. He has demonstrated uneventful defect healing as evidenced by plain radiography and functional assessment.



Fig 3. A chronic infected nonunion developed post Grade IIIB open tibia-fibula fracture (A). The excised infected bone resulted in an iatrogenic segmental deficiency, which was treated with a cylindrical titanium cage in combination with allograft-DBM, and stabilized with an intramedullary nail. The defect healing progression at 3 months post defect reconstruction surgery (B,C), and at 12 months defect union is evident on biplanar radiography (D,E).

Enhancement of Study Enrollment:

The study PIs identified 2 additional eligible patients who are now in the phase of antibiotic therapy for chronic infection/osteomyelitis. These patients have been informed about study participation, and their successful enrollment is expected once their clinical status meets the study eligibility.

Eligible patient identification and enrollment for the trial are actively ongoing. Although it picked its pace, it progresses slower than expected. The PIs keep soliciting referrals of the eligible patients from UTMB satellite out- and inpatient clinic locations. The PIs' institution recently expanded its clinical enterprise to include new out- and inpatient treatment sites, and this is expected to enhance eligible patient referral and recruitment.

4. Key Research Accomplishments

The clinical trial is ongoing.

UTMB IRB approvals/renewals have been obtained for study continuation.

The trial is conducted in accordance with the IRB-approved protocol, and the trial progresses uneventfully since the last annual report.

5. Conclusion

Study enrollment has improved but remains slow. Improving patient accrual will continue by enhancing referrals of eligible patients from the UTMB main and satellite clinic sites. The study has enrolled 16 patients to date, of whom 2 successfully finished the trial, 3 were withdrawn, and 11 are actively participating. Since the last annual report 8 additional patients were enrolled and they all remain as active study subjects. The followup of all enrolled patients in progressing uneventfully. No study protocol deviations have occurred. There have been 2 adverse events encountered, of which one resulted in patient's discontinuation in the study. All patients are doing well. The patients who completed the study are very satisfied with the outcome. To reduce the incidence of AEs, the PIs critically review each eligible patient for compliance.

Initial radiographic and functional outcomes of limb/defect healing for patients treated with both the Masquelet (Arm I) and the cage (Arm II) techniques are very favorable.

Utilizing the UTMB's EPIC electronic medical records facilitates planning the patients' followup clinic visits, informing/reminding the enrolled patients about the study participation and filling out the questionnaires. Using recently adopted the reloadable ClinCard reimbursement system streamlines and simplifies the process of patient reimbursement for study participation and compliance with the timeframe of the followup visits.

6. Publications, Abstracts, and Presentations

Lindsey RW, Gugala Z. The Comparative Efficacy of the Masquelet Technique versus Titanium Mesh Cage Technique in the Reconstruction of Segmental Bone Defects. A DoD-UTMB Clinical Trial. Baylor College of Medicine Grand Rounds, Houston, TX, on Oct 10, 2014.

Lindsey RW, Gugala Z. A DoD-UTMB Clinical Trial Determining the Efficacy of the Masquelet Technique versus Titanium Mesh Cage Technique in the Reconstruction of Segmental Bone Defects. UTMB Monthly Conference, Victory Lakes, TX, on Jan 21, 2015.

Lindsey RW. Managing post-traumatic femoral bone defects. The UCSF Annual International Orthopaedic Trauma Course. San Francisco, CA. April 28, 2016.

Lindsey RW, Gugala Z. New Horizons: Experience with the Bone Cage. The 26th Annual Meeting of the Baltimore Limb Deformity Course: Masters of Disaster Managing Osteomyelitis in the 21st Century. Baltimore, MD. August 25, 2016.

Lindsey RW. Titanium Cages: How We Can Enhance Their Success. The Annual Meeting of the Orthopaedic Trauma Association. National Harbor, MD. October 5-8, 2016.

7. Inventions, Patents and Licenses

Nothing to report.

8. Reportable Outcomes

Nothing to report.

9. Other Achievements

Nothing to report.

10. References

Nothing to report.

11. Appendices

Nothing to report.